

Docket No. 10806-129

CERTIFICATE OF MAILING

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450; Alexandria, VA 22313-1450 on June 23, 2003.

Holly D. Kegley

108
#16
7/7/03
PATENT
NN

RECEIVED
JUN 27 2003
TECH CENTER 1600/2800

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant: Ib Mendel-Hartvig et al : Paper No.:

Serial No.: 09/582,734 : Group Art Unit: 1641

Filing Date: October 6, 2000 : Examiner: G. Counts

For: **Analytical Method Comprising Addition in Two or More Positions and a Device and Test Kit Therefor**

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The present Appeal Brief is submitted in support of the Notice of Appeal filed by Certificate of Mail on April 17, 2003 and received by the U.S. Patent and Trademark Office on April 22, 2003.

RECEIVED
JUN 26 PM 2:38
COURT OF FEDERAL APPEALS
AND RELATED AUTHORITIES

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee of the present application, Pharmacia Diagnostics AB, by virtue of the Assignment from the inventors to Pharmacia & Upjohn Diagnostics AB and the change of name of Pharmacia & Upjohn Diagnostics AB to Pharmacia Diagnostics AB.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants, the Appellants' undersigned legal representative or the assignee which will directly effect or be directly effected by or having a bearing on the Board's decision in the present appeal.

III. STATUS OF THE CLAIMS

Claims 1-4 and 6-33 are pending and stand rejected. Claim 5 is cancelled. A complete copy of the pending claims is set forth in the Appendix.

IV. STATUS OF AMENDMENT FILED SUBSEQUENT TO REJECTION ON APPEAL

An Amendment Under 37 C.F.R. §1.116 was filed by Certificate of Mailing on February 18, 2003. The Advisory Action dated April 7, 2003 indicated that for purposes of appeal, the Amendment would not be entered, without specifying any reason for refusal of entry of the Amendment.

V. SUMMARY OF THE INVENTION

The present invention is directed to methods for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I) (see, for example, claim 1 and the specification at page 1, lines 5-10). The present invention is also directed to devices for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I), and kits including such devices (see, for example, claims 18 and 32 and the specification at page 18, lines 9-13).

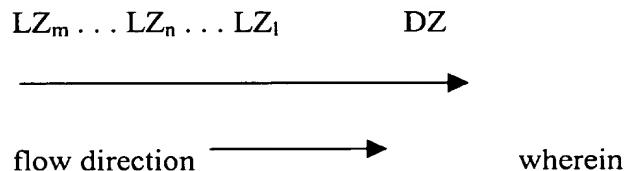
More specifically, according to claim 1, the claimed method is for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I). The flow matrix comprises

A) an application zone for liquid (LZ), containing buffer and sample and optionally reactants needed for a complete determination, but not Reactant I,

B) a detection zone (DZ) with the firmly anchored reactant (Reactant I) located downstream of LZ, and

C) optionally one or more zones in which any of the reactants needed for a complete determination, but not Reactant I, has been pre-deposited.

The flow towards the detection zone is initiated by addition of the liquid with sample in the application zone LZ for transport of analyte and reactants towards the detection zone (DZ), and the amount of the Reactant* bound to DZ is detected, wherein the detected amount is correlated to the amount of analyte in the sample. The flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other:



a) LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n,

b) m is the total number of application zones in which flow is initiated (m≥2),

c) one LZ_n is an application zone for sample (LZ_n·S) and one LZ_n is for Reactant* (LZ_n·R*) with n'' ≥ n';

d) → is the direction of the flow, and

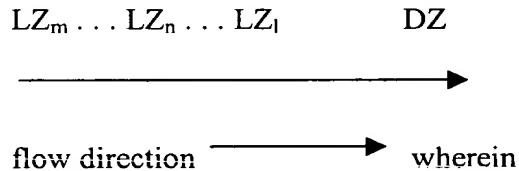
e) DZ is the detection zone.

Flow is initiated by adding liquid to each zone $LZ_m \dots LZ_n \dots LZ_1$ ($m \neq n$) in such a way that liquid_{n+1}, added to the application zone LZ_{n+1} , contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after liquid_n added to the nearest downstream application zone LZ_n .

The device of claim 18 is for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I). The device comprises a flow matrix having:

- A) an application zone for liquid (LZ), containing buffer and sample and optionally reactants needed for a complete determination, but not Reactant I,
- B) a detection zone (DZ) with the firmly anchored reactant (Reactant I) located downstream of LZ, and
- C) optionally one or more zones in which any of the reactants has been pre-deposited.

The flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other:



- a) LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n ,
- b) m is the total number of application zones in which flow is initiated ($m \geq 2$),
- c) one LZ_n is an application zone for sample ($LZ_n \cdot S$) and one LZ_n is for Reactant* ($LZ_n \cdot R^*$) with $n'' \geq n'$;
- d) \longrightarrow is the direction of the flow, and
- e) DZ is the detection zone.

The device is adapted, when flow is initiated by adding liquid to each zone $LZ_m \dots LZ_n \dots LZ_1$ ($m \neq n$) in such a way that liquid_{n+1} added to the application zone LZ_{n+1} , contacts the flow matrix substantially simultaneously to transport the liquid_{n+1} through the matrix immediately after liquid_n, added to the nearest downstream application zone LZ_n .

Claims 2-17 and 19-31 further define the respective method and device. According to claims 2 and 19, $n'' > n'$, i.e., Reactant* is added at a liquid application zone upstream of the sample liquid application zone. According to claims 3 and 20, $n'' = n'$, i.e., the Reactant* liquid application zone coincides with the sample liquid application zone.

According to claims 4 and 21, the Reactant* is pre-deposited in its application zone ($LZ_n''R^*$). According to claims 6 and 22, LZ_{n+1} finishes where LZ_n starts ($m \neq n$), i.e., there are at least two separate liquid application zones immediately adjacent one another.

According to claim 7, application of liquid is performed simultaneously in all $LZ_m \dots LZ_n \dots LZ_1$, i.e., in all liquid application zones, in the method of claim 1.

According to claims 8 and 23, $m \leq 6$; n' is 1, 2 or 3, $n'' > n'$; and $LZ_{n'+1}$, $LZ_{n'+2}$, $LZ_{n'+3}$, $LZ_{n'-1}$, and $LZ_{n'-2}$ are application zones for liquids intended for transport of Reactant* or other reactant or buffer without reactant. According to claims 13 and 27, $m \leq 6$ and n' for the application zone for sample ($LZ_n''S$) is 1, 2 or 3.

According to claims 9 and 25, at least one of the zones $LZ_m \dots LZ_n \dots LZ_1$ comprises a pad or material layer applied on the flow matrix. According to claims 10 and 24, the zones $LZ_m \dots LZ_n \dots LZ_1$ have zone spacers between each other.

According to claim 11, a composition of transported components from an application zone LZ_n is not the same as from the nearest adjacent application zone LZ , in which flow is initiated, (LZ_{n+1} and LZ_{n-1}).

Claims 12 and 26 recite that at least one reactant, other than Reactant*, is pre-deposited in an application zone $LZ_n \dots R$ for liquid intended for transport of the reactant.

Claim 14 recites that the Reactant* has biospecific affinity for the analyte so that Reactant* is incorporated into a complex Reactant'---Analyte---Reactant* in the detection zone in an amount related to the amount of analyte in the sample. Reactant' has biospecific affinity to the analyte and is (a) Reactant I, or (b) a reactant to which Reactant I exhibits biospecific affinity and which is transported from LZ_nS or from an application zone downstream of LZ_nS.

According to claim 15, the matrix comprises at least one calibrator zone (CZ), in which calibrator is bound to, or in advance has been bound to, the matrix. According to claim 29, the flow matrix comprises at least one calibrator zone CZ, in which a calibrator or a binder for the calibrator is firmly anchored in the matrix. Claims 16 and 30 recite that the calibrator zone or zones (CZ) of claims 15 and 29, respectively, have a binder for the calibrator firmly anchored in the matrix, the calibrator optionally being pre-deposited in the matrix upstream of the calibrator zone or zones.

According to claims 17 and 31, the method is performed as part of diagnosing allergy or autoimmune disease and the device is intended for diagnosing allergy or autoimmune disease.

According to claim 28, the detection zone DZ comprises firmly anchored Reactant I, and a reactant to which Reactant I exhibits biospecific affinity optionally is pre-deposited in LZ_nS or in an application zone downstream of LZ_nS.

Finally, claim 32 recites a test kit, comprising (i) a device according to claim 18, and (ii) Reactant*. According to claim 33, the kit additionally comprises (iii) a calibrator when a binder for the calibrator is firmly anchored in the matrix.

VI. ISSUES ON APPEAL

The following four issues are presented on appeal for review by the Board:

- A. The rejection of claims 12 and 18 under 35 U.S.C. §112, second paragraph, as being indefinite;
- B. The rejection of claims 1-4, 6-14, 18-28, 32 and 33 under 35 U.S.C. §102(b) as being anticipated by the Dafforn et al U.S. Patent No. 4,981,786;
- C. The rejection of claims 15, 16, 29 and 30 under 35 U.S.C. §103(a) as being unpatentable over Dafforn et al in view of the Robinson et al published PCT application WO 95/16914; and
- D. The rejection of claims 17 and 31 under 35 U.S.C. §103(a) as being unpatentable over Dafforn et al in view of the Self U.S. Patent No. 4,446,231.

VII. GROUPING OF THE CLAIMS

With respect to the above-noted issues o appeal, Appellants take the following positions:

- A. Appellants submit that with respect to issue A, claims 12 and 18 do not stand or fall together. Reasons in support of the independent patentability of the respective claims are set forth below.
- B. Appellants submit that with respect to issue B, claims 2, 6, 8, 10, 11, 12, 19, 22, 23, 26 and 33 do not stand or fall together with claim 1 or 18 from which they respectively depend. Reasons in support of the independent patentability of these claims are set forth below. Appellants concede that with respect to issue B, claims 3, 4, 7, 9 13, 14, 18, 20, 21, 24, 25, 27, 28 and 32 stand or fall together with claim 1 or 18 from which they respectively depend.
- C. Appellants submit that with respect to issue C, claims 15, 16, 29 and 30 do not stand or fall together. Reasons in support of the independent patentability of these claims are set forth below.

D. Appellants concede that with respect to issue D, claims 17 and 31 stand or fall together.

VIII. ARGUMENTS

As will be set forth in detail below, claims 12 and 18 are definite, and the methods, devices and kits defined by claims 1-4, 6-14, 18-28, 32 and 33 are not anticipated by Dafforn et al. Moreover, the methods and devices defined by claims 15, 16, 29 and 30 are nonobvious over and patentably distinguishable from Dafforn et al in combination with Robinson et al and the methods and devices defined by claims 17 and 31 are nonobvious over and patentably distinguishable from Dafforn et al in combination with Self. Accordingly, the rejections under 35 U.S.C. §§102, 103 and 112, second paragraph, should be reversed.

Favorable action by the Board is respectfully requested.

A. Claims 12 and 18 are Definite

Claims 12 and 18 particularly point out and distinctly claim the subject matter of the invention in accordance with 35 U.S.C. §112, second paragraph.

1. The Examiner's Position

With respect to claim 12, the Examiner asserted in the Official Action dated November 18, 2002 that the "..." at line 3 is vague and unclear. With respect to claim 18, the Examiner asserted in the Official Action dated November 18, 2002 that it is unclear what the term "adapted" in part (e) encompasses and how the device is adapted.

2. Claims 12 and 18 are Definite

Claim 12 recites that at least one reactant, other than Reactant*, is pre-deposited in an application zone LZ_n...R for liquid intended for transport of the reactant. Thus, LZ_n...R is the shorthand name for the defined liquid application zone in which the reactant other than Reactant* is predeposited. The Examiner has not indicated what is unclear about this

shorthand name. Moreover, as the definition of the liquid application zone is set forth in the claim, Appellants submit that one of ordinary skill in the art would find the claim to particularly point out and distinctly claim the subject matter of the invention in accordance with 35 U.S.C. §112, second paragraph.

In claim 18, paragraph (e) recites that the device is adapted, when flow is initiated by adding liquid to each zone $LZ_m \dots LZ_n \dots LZ_1$ ($m \neq n$), in such a way that liquid_{n+1} added to the application zone LZ_{n+1} , contacts the flow matrix substantially simultaneously to transport the liquid_{n+1} through the matrix immediately after liquid_n, added to the nearest downstream application zone LZ_n . Thus, the device is adapted, i.e., is configured, such that liquid_{n+1} added to the application zone LZ_{n+1} , contacts the flow matrix substantially simultaneously to transport the liquid_{n+1} through the matrix immediately after liquid_n, added to the nearest downstream application zone LZ_n . The present specification clearly describes examples of this adaptation, for example at page 20, line 13 - page 21, line 5; page 24, line 31 - page 25, line 7; and page 28, lines 1-22, wherein spacers in the form of strips are provided to form spaced liquid application zones to which liquids may be applied simultaneously via a multichannel pipette. Appellants submit therefore that one of ordinary skill in the art would find the claim to particularly point out and distinctly claim the subject matter of the invention in accordance with 35 U.S.C. §112, second paragraph.

Accordingly, the rejection of claims 12 and 18 under 35 U.S.C. §112, second paragraph, should be reversed.

B. Claims 1-4, 6-14, 18-28, 32 and 33 are Not Anticipated by Dafforn et al

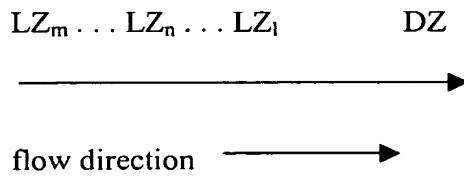
The methods and devices of claims 1-4, 6-14, 18-28, 32 and 33 are not anticipated by Dafforn et al, and are patentably distinguishable therefrom.

1. The Examiner's Position

The Examiner asserted that Dafforn et al disclose an immunoassay device and method for determining an analyte in a sample, employing a first means for introducing a sample into the device and a second means for introducing a liquid reagent other than the sample into the device upstream of the sample, with both application zones located upstream of an immunosorbing detection zone. The Examiner further asserted that Dafforn et al disclose specific binding members immobilized in the immunosorbing zone and that the application of liquid can be performed simultaneously in the application zones, referring to column 24, lines 30-32 of Dafforn et al.

2. The Claimed Methods and Devices are Not Anticipated

More particularly, as defined by claims 1 and 18, the present invention is directed to methods and devices for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I). The flow matrix comprises an application zone for liquid (LZ) containing buffer and sample and optionally reactants needed for a complete determination, but not Reactant I, a detection zone with Reactant I located downstream of LZ, and optionally one or more zones in which any of the reactants has been pre-deposited. The flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other :



wherein LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n, m is the total number of application zones in which flow is initiated ($m \geq 2$), one LZ_n is an application zone for sample (LZ_n·S) and one LZ_n is for Reactant* (LZ_n·R*), with $n'' \geq n'$,

→ is the direction of the flow, and DZ is the detection zone. In the method of claim 1, flow is initiated by adding liquid to each zone LZ_m . . . LZ_n . . . LZ₁ (m≠n) in such a way that liquid_{n+1}, added to the application zone LZ_{n+1}, contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after liquid_n added to the nearest downstream application zone LZ_n. According to claim 18, the device is adapted, when flow is initiated by adding liquid to each zone LZ_m . . . LZ_n . . . LZ₁ (m≠n), in such a way that liquid_{n+1} added to the application zone LZ_{n+1}, contacts the flow matrix substantially simultaneously to transport the liquid_{n+1} through the matrix immediately after liquid_n, added to the nearest downstream application zone LZ_n.

The present methods and devices, allowing substantially simultaneous liquid applications but conducting sequential liquid transport in a manner preserving the order of liquid application zones, facilitate automation of analyte determination, avoid the need for sequential addition of sample and analytically detectable reactant, and allow for predeposited analytical reactant for such methodologies. The presently claimed methods and devices are not taught by Dafforn et al.

Dafforn et al disclose a multiple port assay device. Delivery of a sample may be made into the device through a first means or second means using a dropper, syringe needle, etc., resulting in deposit of the sample on a bibulous strip, and a liquid reagent other than sample may be added to the device. Additional liquid reagents may be added to the device either before or after sample addition, at least one of such reagents being added through the means not used for adding the sample (column 13, lines 32-42). The application of reagents can also be done by breaking an internal liquid-containing container (column 23, line 52).

However, Appellants find no teaching or suggestion by Dafforn et al relating to a method or device as presently claimed wherein at least one biospecific affinity reactant (Reactant I) is firmly anchored in the flow matrix and at least one biospecific affinity reactant

is applied to an application zone in combination with a flow matrix arrangement as recited in claims 1 and 18. Particularly, Appellants find no teaching or suggestion by Dafforn et al of a method or device wherein flow is initiated by adding liquid to each zone in such a way that liquid_{n+1} added to the application zone LZ_{n+1} contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after liquid_n, added to the nearest downstream application zone LZ_n.

In fact, the only specific mention of simultaneous application which Appellants find in the teachings of Dafforn et al is at column 24, beginning at line 22 wherein an assay is described as conducted by adding a sample suspected of containing human chorionic gonadotrophin (HCG) at a first opening and simultaneously adding a developer solution containing enzyme substrate at the second opening. However, contrary to the present methods and device wherein liquid_{n+1} added to the application zone LZ_{n+1} contacts the flow matrix *substantially simultaneously* and is transported through the matrix *immediately after* liquid_n, added to the nearest downstream application zone LZ_n, Dafforn et al disclose that the sample HCG binds to an enzyme conjugate and the resulting complex is carried by the moving developer solution to the detection zone where it binds, i.e., where the complex binds to the detection zone. Thus, Appellants find no teaching or suggestion by Dafforn et al that liquid reagent added *simultaneously* with a sample is transported through a matrix *immediately after* the sample. Rather, Dafforn et al teach that HCG-conjugate complex is carried by the moving developer solution to the detection zone. Dafforn et al provide no teaching or suggestion relating to simultaneous application with a sequential flow of reagents through a matrix.

Thus, in the present methods and devices, sample and reagent may be applied to the flow matrix simultaneously. The sample begins migration to the detection zone and is followed by liquid migration from the next upstream zone. As a result, there is a continuous

migration of sample and reagents through the flow matrix, started by one initial application occasion. The flow of liquids through the flow matrix and the detection zone is in the same order as the liquid application zones. Appellants find no such teachings by Dafforn et al.

In the Advisory Action, the Examiner appeared to assert that because the present claims encompass the embodiment wherein $n=n'$, i.e., the Reactant* liquid application zone coincides with the sample application zone, Dafforn et al's embodiment at column 24 anticipates the claimed methods and devices. Appellants submit however that Dafforn et al do not anticipate even this embodiment of the claimed invention, i.e., where $n=n'$. That is, even in this embodiment, both of claims 1 and 18 require that there are at least two liquid application zones in which flow is initiated, i.e., $m \geq 2$, and that the respective liquids applied to such zones substantially simultaneously are transported through the flow matrix in the respective order of the liquid application zones, i.e., wherein flow is initiated by adding liquid to each zone in such a way that liquid_{n+1} added to the application zone LZ_{n+1} contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after liquid_n, added to the nearest downstream application zone LZ_n. In contrast, Dafforn et al teach that the developer solution applied at a second opening carries a complex of HCG applied at a first opening and enzyme conjugate to the detection zone, i.e., the liquids applied simultaneously at the first and second openings mix prior to their travel to the detection zone and the upstream liquid is not transported through the matrix immediately after liquid added to the nearest downstream application zone.

The Examiner further asserted in the Advisory Action that developer added after the complex would follow the complex. However, such an embodiment, even if taught by Dafforn et al, does not anticipate the present methods and devices as claim 1 recites that flow is initiated by adding liquid to each zone LZ_m . . . LZ_n . . . LZ₁ ($m \neq n$) in such a way that liquid_{n+1}, added to the application zone LZ_{n+1}, contacts the flow matrix *substantially*

simultaneously and is transported through the matrix *immediately after* liquid_n added to the nearest downstream application zone LZ_n. Similarly, according to claim 18, the device is adapted, when flow is initiated by adding liquid to each zone LZ_m . . LZ_n . . LZ₁ (m≠n), in such a way that liquid_{n+1} added to the application zone LZ_{n+1}, contacts the flow matrix *substantially simultaneously* to transport the liquid_{n+1} through the matrix *immediately after* liquid_n, added to the nearest downstream application zone LZ_n. The embodiment proposed by the Examiner does not employ substantially simultaneous liquid contact, particularly with transport immediately after, as presently claimed.

Anticipation under 35 U.S.C. §102 requires that each and every element set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q.2d 1949, 1950 (Fed Cir. 1999). In view of the deficiencies in the teachings of Dafforn et al with respect to simultaneous application and sequential transport, Dafforn et al do not anticipate the present claims under 35 U.S.C. §102. It is therefore submitted that the rejection under 35 U.S.C. §102 based on Dafforn et al should be reversed.

3. Claims 2, 8, 19 and 23 are Further Patentably Distinguishable

According to claims 2 and 19, n" > n'. According to claims 8 and 23, m≤6; n' is 1, 2 or 3, n" > n'; and LZ_{n'+1}, LZ_{n'+2}, LZ_{n'+3}, LZ_{n'-1}, and LZ_{n'-2} are application zones for liquids intended for transport of Reactant* or other reactant or buffer without reactant. Thus, according to all of these claims, n">n', i.e., Reactant* is added at a liquid application zone LZ_{n''R*} upstream of the sample liquid application zone LZ_{n'S}.

Appellants find no teaching by Dafforn et al of a method or a device wherein a liquid application zone for analytically detectable reactant, i.e., Reactant*, is upstream of a liquid application zone for sample and the liquids are applied substantially simultaneously to the flow matrix. The only teaching Appellants find in Dafforn et al of simultaneous liquid application employs conjugate at the sample application zone and a developer containing

enzyme substrate is applied simultaneously with the sample. Such a disclosure does not anticipate the embodiments of claims 2, 8, 19 or 23. Thus, these claims are further patentably distinguishable from the teachings of Dafforn et al and the rejection under 35 U.S.C. §102 should be reversed.

4. Claims 6 and 22 are Further Patentably Distinguishable

According to claims 6 and 22, LZ_{n+1} finishes where LZ_n starts ($m \neq n$), i.e., there are at least two separate liquid application zones immediately adjacent one another.

Appellants find no teaching by Dafforn et al of a device or method as defined by claims 6 and 22, wherein two zones immediately adjacent one another can provide for sequential transport of substantially simultaneously applied liquids. In fact, the teachings of Dafforn et al are in opposite in that Dafforn et al teach mixing of simultaneously applied liquids, without indicating if the first and second openings discussed at column 24 are immediately adjacent one another or not. Thus, these claims are further patentably distinguishable from the teachings of Dafforn et al and the rejection under 35 U.S.C. §102 should be reversed.

5. Claims 10 and 24 are Further Patentably Distinguishable

According to claims 10 and 24, the zones $LZ_m \dots LZ_n \dots LZ_1$ have zone spacers between each other. As is described in the specification, the zone spacers are one manner in which the sequential transport of substantially simultaneously applied liquids may be obtained. See, for example, the specification at page 20, line 13 - page 21, line 5; page 24, line 31 - page 25, line 7; and page 28, lines 1-22, wherein zone spacers in the form of strips are provided to form spaced liquid application zones to which liquids may be applied simultaneously via a multichannel pipette.

Appellants find no teaching by Dafforn et al regarding such zone spacers, or any reason to provide such zone spacers. Thus, these claims are further patentably

distinguishable from the teachings of Dafforn et al and the rejection under 35 U.S.C. §102 should be reversed.

6. Claim 11 is Further Patentably Distinguishable

According to claim 11, a composition of transported components from an application zone LZ_n is not the same as from the nearest adjacent application zone LZ, in which flow is initiated, (LZ_{n+1} and LZ_{n-1}).

Appellants find no teaching or suggestion by Dafforn et al of a method as recited in claim 11 wherein a composition of transported components from an application zone LZ_n is not the same as from the nearest adjacent application zone LZ, in which flow is initiated, (LZ_{n+1} and LZ_{n-1}). In fact, the teachings of Dafforn et al at column 24 are opposite to the requirements of claim 11 in that Dafforn et al teach mixing of the components from adjacent application areas, namely developer and complex. Thus, this claim is further patentably distinguishable from the teachings of Dafforn et al and the rejection under 35 U.S.C. §102 should be reversed.

7. Claims 12 and 26 are Further Patentably Distinguishable

Claims 12 and 26 recite that at least one reactant, other than Reactant*, is pre-deposited in an application zone LZ_{n...R} for liquid intended for transport of the reactant.

Appellants find no teaching or suggestion by Dafforn et al of a second reactant pre-deposited in a liquid application zone for transport. The embodiment described at column 24 of Dafforn et al employs a single pre-deposited enzyme- anti-HCG conjugate, intended for complexing and transport. However, Appellants find no teaching by Dafforn et al of any other pre-deposited reactant for transport. Thus, these claims are further patentably distinguishable from the teachings of Dafforn et al and the rejection under 35 U.S.C. §102 should be reversed.

8. Claim 33 is Further Patentably Distinguishable

Finally, claim 33 is directed to a test kit, comprising (i) a device according to claim 18, and (ii) Reactant*, and additionally (iii) a calibrator when a binder for the calibrator is firmly anchored in the matrix.

Appellants find no teaching by Dafforn et al of a calibrator, or any binder for a calibrator, or for providing a calibrator in kit form with a device as defined in claim 18 and Reactant*. In view of Dafforn et al's complete failure to teach or suggest a device including calibrator, Dafforn et al do not anticipate claim 33. Thus, this claim is further patentably distinguishable from the teachings of Dafforn et al and the rejection under 35 U.S.C. §102 should be reversed.

C. Claims 15, 16, 29 and 30 are Not Rendered Obvious

The methods and devices of claims 15, 16, 29 and 30 are nonobvious over and patentably distinguishable from Dafforn et al in view of Robinson et al.

1. The Examiner's Position

The Examiner relied on Robinson et al as disclosing the use of calibration zones. The Examiner asserted it would have been obvious to incorporate the use of a calibrator zone as taught by Robinson et al in the method and device of Dafforn et al.

2. The Combination Does Not Render the Claims Obvious

Claims 15 and 16 depend directly and indirectly, respectively, from claim 1 while claims 29 and 30 depend directly and indirectly, respectively, from claim 18. According to claim 15, the matrix comprises at least one calibrator zone (CZ), in which calibrator is bound to, or in advance has been bound to, the matrix. According to claim 29, the flow matrix comprises at least one calibrator zone CZ, in which a calibrator or a binder for the calibrator is firmly anchored in the matrix. Claims 16 and 30 recite that the calibrator zone or zones (CZ) of claims 15 and 29, respectively, have a binder for the calibrator firmly anchored in the

matrix, the calibrator optionally being pre-deposited in the matrix upstream of the calibrator zone or zones.

The deficiencies of Dafforn et al noted in detail above with respect to claims 1 and 18 apply equally well with respect to claims 15, 16, 29 and 30. Moreover, Appellants find no teaching or suggestion by Dafforn et al relating to calibration, particularly, integral with their device, or relating to a calibration zone in their device, calibrator predeposited in or applied to a matrix, or a binder for a calibrator in a calibration zone.

The deficiencies of Dafforn et al are not resolved by Robinson et al. Robinson et al describe a sensor device for a sandwich assay comprising a discrete zone having a measurement region on which is immobilized a first specific binding partner for a ligand under assay and a known amount of a releasable optionally labeled second specific binding partner for the ligand under assay, and a second discrete zone having a region on which is immobilized a first specific binding partner for the ligand under assay, a releasable known amount of ligand analog, and a second known amount of a second optionally labeled second specific binding partner for the ligand under assay.

However, Appellants find no teaching or suggestion by Robinson et al of a method or device as recited in claims 1 and 18, respectively, employing at least one analytically detectable biospecific affinity reactant (Reactant*) and at least one firmly anchored biospecific affinity reactant (Reactant I) in a detection zone, with the arrangement of liquid application zones and liquid flows as recited in claims 1 and 18. Additionally, Appellants find no teaching or suggestion for employing any of the elements of Robinson et al's sensor device in the multiple port assay device of Dafforn et al. In fact, while Dafforn et al require application of one or more liquid reagents in addition to a liquid sample through different introduction means, the sensor device of Robinson et al is designed for a sandwich assay wherein only a sample containing a ligand under assay is applied.

Appellants are not claiming the use of calibrator per se. Rather, Appellants are claiming defined methods and devices, in which the flow matrix comprises at least one calibrator zone (CZ), in which calibrator is bound to, or in advance has been bound to, the matrix (claim 15) or in which a calibrator or a binder for the calibrator is firmly anchored in the matrix (claim 29), and optionally which have a binder for the calibrator firmly anchored in the matrix, the calibrator optionally being pre-deposited in the matrix upstream of the calibrator zone or zones (claims 16 and 30). Appellants find no teaching or suggestion for modifying the teachings of Dafforn et al to include any portion of the Robinson et al teachings, and particularly those which would relate to calibration zones, calibrator and binder as recited in the present claims, to arrive at the invention defined by any of claims 15, 16, 29 or 30.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). In view of the failure of Robinson et al to resolve the deficiencies of Dafforn et al, particularly with respect to a method and device allowing simultaneous application and sequential transport, or to provide any suggestion for combining and modifying the teachings of Robinson et al and Dafforn et al along the lines asserted by the Examiner, the combination of these references does not enable one of ordinary skill in the art to conduct the claimed method or make and use the claimed device. Thus, the combination of Dafforn et al and Robinson et al does not render the present claims obvious, and the rejection under 35 U.S.C. §103 should be reversed.

D. Claims 17 and 31 are Not Rendered Obvious

The methods and devices of claims 17 and 31 are nonobvious over and patentably distinguishable from Dafforn et al in view of Self.

1. The Examiner's Position

The Examiner relied on Self as disclosing that immunoassays are used for the detection and/or determination of autoimmune diseases. The Examiner asserted it would have been obvious to use immunoassays as taught by Self for the diagnosis of autoimmune diseases.

2. The Combination Does Not Render the Claims Obvious

Claim 17 depends directly from claim 1 while claim 31 depends directly from claim 18. These claims recite respectively that the method is performed as part of diagnosing allergy or autoimmune disease and that the device is intended for diagnosing allergy or autoimmune disease.

The deficiencies of Dafforn et al noted in detail above with respect to claims 1 and 18 apply equally well with respect to claims 17 and 31. Moreover, Appellants find no specific teaching or suggestion by Dafforn et al relating diagnosing allergy or autoimmune disease.

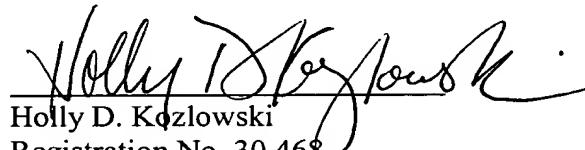
The deficiencies of Dafforn et al are not resolved by Self. That is, while Self discloses an immunoassay using an amplified cyclic detection system, Appellants find no teaching or suggestion by Self relating to a method or device for determination of an analyte in a sample and a flow matrix employing a combination of biospecific affinity reactants and liquid application zones and flow as defined in claims 1 and 18. Similarly, Appellants find no teaching or suggestion by Self for modifying any of the teachings of Dafforn et al to result in either a method or a device as presently claimed. Thus, the mere teaching by Self of the use of immunoassays for detection and/or determination of autoimmune diseases does not resolve the deficiencies of Dafforn et al, particularly with respect to a method and device allowing simultaneous liquid application and sequential liquid transport. Thus, the combination of Dafforn et al and Self does not render the methods and devices of the present claims obvious, and the rejection under 35 U.S.C. §103 should be reversed.

IV. CONCLUSIONS

For the reasons set forth in detail above, claims 12 and 18 are definite, and the methods, devices and kits defined by claims 1-4, 6-14, 18-28, 32 and 33 are not anticipated by Dafforn et al. Moreover, the methods and devices defined by claims 15, 16, 29 and 30 are nonobvious over and patentably distinguishable from Dafforn et al in combination with Robinson et al and the methods and devices defined by claims 17 and 31 are nonobvious over and patentably distinguishable from Dafforn et al in combination with Self. Accordingly, the rejections under 35 U.S.C. §§102, 103 and 112, second paragraph, should be reversed.

Favorable action by the Board is respectfully requested.

Respectfully submitted,

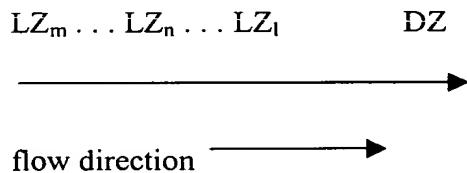

Holly D. Kozlowski
Registration No. 30,468
Dinsmore & Shohl LLP
1900 Chemed Center
255 East Fifth Street
Cincinnati, Ohio 45202
(513) 977-8568

APPENDIX

1. A method for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I), and the flow matrix comprises:

- A) an application zone for liquid (LZ), containing buffer and sample and optionally reactants needed for a complete determination, but not Reactant I,
- B) a detection zone (DZ) with the firmly anchored reactant (Reactant I) located downstream of LZ, and
- C) optionally one or more zones in which any of the reactants needed for a complete determination, but not Reactant I, has been pre-deposited, wherein (i) the flow towards the detection zone is initiated by addition of the liquid with sample in the application zone LZ for transport of analyte and reactants towards the detection zone (DZ), and (ii) the amount of the Reactant* bound to DZ is detected, wherein the detected amount is correlated to the amount of analyte in the sample, wherein

I. the flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other:



wherein

- a) LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n,
- b) m is the total number of application zones in which flow is initiated ($m \geq 2$),

c) one LZ_n is an application zone for sample (LZ_nS) and one LZ_n is for Reactant* (LZ_nR*) with n'' ≥ n';

d) → is the direction of the flow, and

e) DZ is the detection zone, and

II. flow is initiated by adding liquid to each zone LZ_m . . . LZ_n . . . LZ₁ (m ≠ n) in such a way that liquid_{n+1}, added to the application zone LZ_{n+1}, contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after liquid_n added to the nearest downstream application zone LZ_n.

2. The method according to claim 1, wherein n'' > n' (sequential variants regarding analyte and Reactant*).

3. The method according to claim 1, wherein n'' = n' (simultaneous variants regarding analyte and Reactant*).

4. The method according to claim 1, wherein Reactant* is pre-deposited in its application zone (LZ_nR*).

6. The method according to claim 1, wherein LZ_{n+1} finishes where LZ_n starts (m ≠ n).

7. The method according to claim 1, wherein application of liquid is performed simultaneously in all LZ_m . . . LZ_n . . . LZ₁.

8. The method according to claim 1, wherein $m \leq 6$; n' is 1, 2 or 3, $n'' > n'$; $LZ_{n'+1}$, $LZ_{n'+2}$, $LZ_{n'+3}$, $LZ_{n'-1}$, and $LZ_{n'-2}$ are application zones for liquids intended for transport of Reactant* or other reactant or buffer without reactant.

9. The method according to claim 1, wherein at least one of the zones $LZ_m \dots LZ_n \dots LZ_1$ comprises a pad or material layer applied on the flow matrix.

10. The method according to claim 1, wherein the zones $LZ_m \dots LZ_n \dots LZ_1$ have zone spacers between each other.

11. The method according to claim 1, wherein a composition of transported components from an application zone LZ_n is not the same as from the nearest adjacent application zone LZ , in which flow is initiated, (LZ_{n+1} and LZ_{n-1}).

12. The method according to claim 1, wherein at least one reactant, other than Reactant*, is pre-deposited in an application zone $LZ_n \dots R$ for liquid intended for transport of the reactant.

13. The method according to claim 1, wherein $m \leq 6$ and n' for the application zone for sample ($LZ_n S$) is 1, 2 or 3.

14. The method according to claim 1, wherein Reactant* has biospecific affinity for the analyte so that Reactant* is incorporated into a complex Reactant'---Analyte---Reactant* in the detection zone in an amount related to the amount of analyte in the sample, in which complex Reactant' has biospecific affinity to the analyte and is

- (a) Reactant I, or
- (b) a reactant to which Reactant I exhibits biospecific affinity and which is transported from LZ_nS or from an application zone downstream of LZ_nS.

15. The method according to claim 1, wherein the matrix comprises at least one calibrator zone (CZ), in which calibrator is bound to, or in advance has been bound to the matrix.

16. The method according to claim 15, wherein the calibrator zone or zones (CZ) have a binder for the calibrator firmly anchored in the matrix, the calibrator optionally being pre-deposited in the matrix upstream of the calibrator zone or zones.

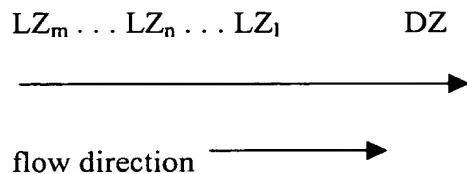
17. The method according to claim 1, wherein the method is performed as part of diagnosing allergy or autoimmune disease.

18. A device for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I), said device comprising a flow matrix having:

- A) an application zone for liquid (LZ), containing buffer and sample and optionally reactants needed for a complete determination, but not Reactant I,
- B) a detection zone (DZ) with the firmly anchored reactant (Reactant I) located downstream of LZ, and
- C) optionally one or more zones in which any of the reactants has been pre-deposited,

wherein

the flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other:



wherein

- a) LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n ,
- b) m is the total number of application zones in which flow is initiated ($m \geq 2$),
- c) one LZ_n is an application zone for sample ($LZ_n \cdot S$) and one LZ_n is for Reactant* ($LZ_n \cdot R^*$) with $n'' \geq n'$;
- d) \longrightarrow is the direction of the flow, and
- e) DZ is the detection zone, wherein the device is adapted, when flow is initiated by adding liquid to each zone $LZ_m \dots LZ_n \dots LZ_1$ ($m \neq n$) in such a way that liquid _{$n+1$} added to the application zone LZ_{n+1} , contacts the flow matrix substantially simultaneously to transport the liquid _{$n+1$} through the matrix immediately after liquid _{n} , added to the nearest downstream application zone LZ_n .

19. The device according to claim 18, wherein $n'' > n'$ and the device is intended for sequential transport of analyte and Reactant*.

20. The device according to claim 18, wherein $n'' = n'$ and the device is intended for simultaneous transport of analyte and Reactant*.

21. The device according to claim 18, wherein Reactant* is pre-deposited in its application zone ($LZ_{n''}R^*$).

22. The device according to claim 18, wherein LZ_{n+1} finishes where LZ_n starts ($m \neq n$).

23. The device according to claim 18, wherein $m \leq 6$; n' is 1, 2 or 3; $n'' > n$; $LZ_{n'+1}$, $LZ_{n'+2}$, $LZ_{n'+3}$, $LZ_{n'-1}$, and $LZ_{n'-2}$ are application zones for liquids intended for transport of Reactant* or other reactant or buffer without reactant.

24. The device according to claim 18, wherein the zones LZ_m . LZ_n . LZ_l have zone spacers between each other.

25. The device according to claim 18, wherein at least one of the zones LZ_m . . LZ_n . . LZ_l comprises a pad or material layer applied on the flow matrix.

26. The device according to claim 18, wherein at least one reactant, other than Reactant*, is pre-deposited in an application zone $LZ_{n''}R$ for liquid intended for transport of the reactant.

27. The device according to claim 18, wherein $m \leq 6$ and n' for the application zone for sample (LZ_nS) is 1, 2 or 3.

28. The device according to claim 18, wherein the detection zone DZ comprises firmly anchored Reactant I, and a reactant to which Reactant I exhibits biospecific affinity optionally is pre-deposited in LZ_nS or in an application zone downstream of LZ_nS.

29. The device according to claim 18, wherein the flow matrix comprises at least one calibrator zone CZ, in which a calibrator or a binder for the calibrator is firmly anchored in the matrix.

30. The device according to claim 29, wherein the calibrator zone or zones (CZ) have a binder for the calibrator firmly anchored in the matrix, and calibrator optionally is pre-deposited in the matrix upstream of the calibrator zone or zones.

31. The device according to claim 18, wherein the device is intended for diagnosing allergy or autoimmune disease.

32. A test kit, comprising (i) a device according to claim 18, and (ii) Reactant*.

33. The test kit according to claim 32, wherein the kit additionally comprises (iii) a calibrator when a binder for the calibrator is firmly anchored in the matrix.

916262